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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/734,281	12/11/2000	Marc Mercken	12546.4USC1	3720

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Attention of Mark T. Skoog
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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 01/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/734,281	MERCKEN ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *29 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,24 and 29-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,24 and 29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. 08/108,758.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10-3-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO AMENDMENT

The amendment filed 8-29-03 and IDS filed 10-03-03 has been entered into the record. Claims 1-20, 22-23 and 25-28 have been cancelled. Claims 21, 24, 29-33 are pending and under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Withdrawn

The art rejections of record are withdrawn based upon Applicants' amendments.

Rejections Maintained

Claims 21, 24, 29, 30 and new claims 31-33 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 18, 19 of U.S. Patent No. 6,121,003.

The terminal disclaimer filed August 11, 2002 was found to be improper because it recited the incorrect serial number in the heading of the terminal disclaimer and the serial number in the heading conflicted with the text of the terminal disclaimer

New Rejections Based on Amendment

Claim 30 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case the claim essentially recites that the monoclonal antibody can bind a phosphorylated serine outside of that designated per SEQ ID NO:1 or SEQ ID NO:2 and as such broadens the subject matter of the independent claim.

Claims 21, 24, and 29-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 21, 24 and 29, the claims are confusing since it is not clear what the phrase "which forms a complex with" modifies. Does it modify the "any other peptide" such that peptide-peptide interactions are encompassed or does it modify the monoclonal antibody that forms an immunological complex with the peptide YSSPGSPGT or the peptide YSSPGSPGT ? It is believed that this issue is best

resolved by amending (b) to recite --or with any other peptide forming an immunological complex with said monoclonal antibody that forms an immunological complex with the peptide YSSPGSPGT or the peptide YSSPGSPGT.--.

As to claim 29, the claim is confusing because it appears to recite at least two elements. However, the claim ends with a full stop after element (a). Further, the lost of elements appears to be incomplete because the list appears incomplete in that it is not apparently listed as elements (a) and (b), but (a).(b). and it is not clear if this is the complete list or an incomplete list of the elements of the kit. This issue is best resolved by amending the claims to eliminate the full stop at the end of element (a) and inserting --and-- between elements (a) and (b).

As to claims 32 and 33, the claims further comprise "a buffer solution" however claim 29 already comprises a buffer solution. Are these additional to the buffer solution already present ? If these are additional solutions, the claims should state " a second buffer solution" and "a third buffer solution". As such, the claims as currently drafted are confusing as whether they recite additional independent buffers or are intended use of the buffer that is already present. Clarification is requested.

The following art rejections are reinstated in view of the amendments to the claims.

Claims 21, 24 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dickson et al (Acta Neuropathol, 73:254-258, 1987 of record in parent prosecution) in view of Kosik et al (Neuron, 1:817-825, 1988) and Binder et al (J. Cell. Biol., 101:1371-1378, October 1985).

Dickson et al teaches using extracts form Alzheimer brain as the immunogen for raising monoclonal antibodies which recognize a phosphorylated epitope present in tau. Dickson et al are silent as to the method used for raising their monoclonal antibodies and the epitopes on tau to which their antibodies bind.

Kosik et al disclose that tau protein has been shown to be an integral component of Alzheimer's paired helical filaments (PHF), they disclose the immunogens used for raising monoclonal antibodies to tau and they disclose a method of defining the antigenic sites that monoclonal antibodies bind within human tau (Figure 3 on page 820). They mapped epitopes for 5 monoclonal antibodies that span almost the entire length of tau suggesting that PHF contain tau in its entirety or nearly in its entirety (Abstract on page 817 and page 822, column 1, second full paragraph) and includes the epitope of monoclonal antibody tau 1 which binds to Pro Lys Ser Gly Asp Arg Ser Gly **Tyr Ser Ser Pro Gly Ser Pro Gly Thr** Pro Gly (Figure 3) that includes the dephosphorylated epitope of claim 22 in bold. Kosik et al disclose that the tau 1 epitope is phosphatase sensitive which has led to the proposal that the molecule might undergo potentially significant conformational changes as the result of the addition or removal of phosphate. Tau 1 recognize

NFT only after treatment with alkaline phosphatase as such has been considered to recognize a site that is aberrantly phosphorylated during the process of NFT formation (page 822, column 2, first full paragraph).

Binder et al disclose producing monoclonal antibodies that binds to tau polypeptides by immunizing mice with bovine microtubule-associated protein, MAP-2, fusing splenocyte with SP/O myeloma cells and testing the resulting hybrid cells form those which produce monoclonal antibodies which bind MAP-2 or tau. One antibody Tau-1 was cross-reactive with rat brain, exhibiting binding to several polypeptides in the tau region of the gel. Binder et al disclose subcloning this cell line then injecting it into a mouse for the production of antibody-containing ascites fluid where cells obtained from the ascites fluid were harvested, cultured and subcloned. Binder et al disclose using monoclonal antibodies in ELISA formats including a competitive format for quantitative determination of tau (page 1372, column 2, third full paragraph).

It would have been prima facie obvious to one having ordinary skill in the art to make additional monoclonal antibodies which bind to phosphorylated epitopes on tau as alternates to the ones taught by Dickson et al for detecting phosphorylated tau and NFT in Alzheimer's disease using the conventional methods as taught by Binder et al because Binder et al teach conventional methods of making hybridoma cell lines which produce monoclonal antibodies and isolated monoclonal antibodies from mouse ascites fluid which bind to tau protein using a variety of immunogens including bovine MAPs, bovine tau, detergent extracts of rat brain protein and Alzheimer basal forebrain and methods for detecting tau using a competitive ELISA format and Dickson teaches that monoclonal antibodies raised against extracts from Alzheimer brain samples recognize a phosphorylated epitope on tau and are used to immunostain brain samples from patients with Alzheimer's disease. Thus, one would have reasonably expected to make other hybridomas with produce monoclonal antibodies which bind to phosphorylated epitopes on abnormally phosphorylated tau present in Alzheimer brain tissue as the functional equivalents of the monoclonal antibody AT8 using known immunogens and conventional methods. One would have been motivated to screen for those monoclonal antibodies which recognize the phosphorylated epitope to which the Tau-1 antibody when that epitope is abnormally phosphorylated as an aide to detecting and diagnosis brain as a means of simplifying Kosik assays because Kosik teaches epitopes on tau which are recognized by monoclonal antibodies including the Tau-1 epitope which is phosphatase -sensitive and only reveled after treatment with alkaline phosphatase, and thus by using an antibody which recognizes the phosphorylated epitope one could eliminate the need to treat the sample with alkaline phosphatase prior to antibody binding. It would also have been obvious to one of ordinary skill in the art to assemble the reagents in a kit format because kits are convenient and economical means of providing the necessary reagents for the user. One would

have been motivated to immobilize those monoclonal antibodies on a solid support for isolating abnormally phosphorylated tau protein from brain samples taken from patients with Alzheimer's disease because affinity purification is conventional used in the art as a means for isolating antigen from a sample.

Claims 29 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dickson et al (Acta Neuropathol, 73:254-258, 1987 of record in parent prosecution), Kosik et al (Neuron, 1:817-825, 1988) and Binder et al (J. Cell. Biol., 101:1371-1378, October 1985) as applied to claims 21, 24 and 30 above and further in view of Trojanowski et al (U.S. Patent 5,601,985, issued Feb 11, 1997 with priority to August 14, 1991) and Catty et al (Antibodies, Volume II A Practical Approach, IRL Press, at Oxford University Press, Oxford, 1990, pages 97-154).

The combination of Dickson et al (Acta Neuropathol, 73:254-258, 1987 of record in parent prosecution), Kosik et al (Neuron, 1:817-825, 1988) and Binder et al (J. Cell. Biol., 101:1371-1378, October 1985) is set forth supra. The combination differs by not including a second monoclonal antibody against a different epitope on tau and buffers for performing the assay.

Trojanowski et al teach monoclonal antibodies that bind to a phosphorylated peptide which corresponds to residues 389-402 of human tau which was selectively phosphorylated at serine position 396, which they term T3P. Trojanowski et al disclose that anti-T3P antibodies were used immunocytochemically to stain tissue sections and in western blot experiments from Alzheimer's disease and control brains where the anti-T3P did not recognize normal tau (page 678, column 1, second paragraph). Trojanowski et al teach that dephosphorylating A68, to which the T3P antibody binds, provides for a drop in electrophoretic mobility with a treatment with a dephosphorylating agent and migrated to a position very close to that of dephosphorylated tau (page 678, column 2, Figure 2A).Trojanowski et al conclude that A68 is in fact derived from tau (see page 678, column 2, second full paragraph). Trojanowski et al teach test kits for diagnosing a disease comprising antigens capable of binding with antibodies reactive with a peptide comprising the sequence of LysSerProVal wherein the ser is phosphorylated or antibodies specifically reactive with the phosphorylated sequence (see column 8, first full paragraph). Trojanowski et al teach that the identification of abnormally phosphorylated tau can be accomplished by enzyme immunoassay (column 7, lines 40-45).. In particular, Trojanowski et al teach that the identification of abnormally phosphorylated tau can be accomplished by enzyme immunoassay (column 7, lines 40-45) and that kits for use in detecting such are contemplated. Trojanowski et al differ by not explicitly teaching a two site ELISA for detection of abnormally phosphorylated tau and its components in a kit.

Dickson et al teach a second monoclonal antibody binding a second phosphorylated epitope on tau.

Catty et al teach a variety of conventional formats for enzyme immunoassays (see page 103, Figure 2). In particular Catty et al teach the two site immunometric assay as a test for antigen where the capture antibody is attached to a solid phase such as a microtiter plate and the second antibody is labeled (see page 104-105). Catty et al teach all the reagents and buffers needed to perform the ELISA (see page 101, Table 2, page 125 and pages 126-133).

It would have been *prima facie* obvious to measure abnormally phosphorylated tau in a sample by means of a two site indirect ELISA according to Catty et al by substituting the art established monoclonal antibodies of Trojanowski et al and the antibody of Dickson et al (Acta Neuropathol, 73:254-258, 1987 of record in parent prosecution), Kosik et al (Neuron, 1:817-825, 1988) and Binder et al (J. Cell. Biol., 101:1371-1378, October 1985) as combined supra in the method as a means of detection of abnormally phosphorylated tau because Trojanowski et al teach that the identification of abnormally phosphorylated tau can be accomplished by enzyme immunoassay already in the art and commercially available (column 7, lines 40-45). Further, it would have been *prima facie* obvious to assemble the all of the necessary reagents (antibody attached to the microtiter plate, multiple buffers, substrates, and developing agents) in a microtiter kit format for convenience and economy for the consumer and to reduce overall processing time for the assay by providing a reduced number of steps (i.e. binding the antibody to the microtiter plate well).

Claims 24, 32 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

As to claim 24, the claim recites in (a) YS*SPGSPGT. This embodiment lacks written description in the specifiation and as such constitutes new matter. This issue is best resolved by Applicants by pointing to page and line number of the specification where written description support for this limitation can now be found.

As to claims 32 and 33, the claims appear to recite kits with second and third buffers. There is no apparent written description support for kits with three independent buffers contained therein. This issue is best resolved by Applicants pointing to the specification by page and line number where written description support for these new embodiments can be found.

Status of Claims

All claims stand rejected.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 703-305-7555 or 571-272-0855 after January 27, 2004. The examiner can normally be reached on M-F 6:30 pm - 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Smith Lynette can be reached on 703-308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patricia A. Duffy
Primary Examiner
Art Unit 1645